REMARKS

Claims 1-27 are pending. Claims 8-11 are under examination.

Claims 8-11 have been amended solely for clarity. The amendments are supported throughout the application as filed, e.g., at page 4, lines 17-24, and page 5, lines 1-8 and 18-23. No new matter has been added.

The invention relates to methods of screening for a test gene that encodes a polypeptide (e.g., an enzyme) that converts a ligand precursor (an inactive form of a nuclear receptor ligand that does not bind to the nuclear receptor) into a ligand (an active form of a nuclear receptor ligand capable of binding and activating the nuclear receptor).

Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 8-11 are rejected as indefinite.

The Examiner asserts that claims 8-11 are incomplete for omitting the essential steps of: "the converted ligand molecule, after conversion to the active form, binds to and activates the nuclear receptor." In response, claims 8-11 have been amended to clarify how the elements of the claim are interrelated. The claims now recite that the increase in activity in the presence of the test agent indicates that the test gene encodes a polypeptide that converts the ligand precursor into a ligand that activates the nuclear receptor.

The Examiner also states that claims 8-11 are vague and indefinite in the recitation of the term "ligand precursor." This aspect of the rejection is respectfully traversed. If the scope of the claimed subject matter can be determined by one having ordinary skill in the art, a rejection for indefiniteness is not appropriate. See MPEP 706.03(d). In this case, the meaning and scope of the term would be readily ascertainable by one of ordinary skill in the art, guided by the specification. Applicants note that the term "ligand" is expressly defined at page 10, lines 1-2, as "a compound that binds to a nuclear receptor and regulates the transcriptional activating ability of a target gene of the nuclear receptor" and the term "precursor" is understood in the biological arts to mean a substance from which a more active or mature substance is formed. See, e.g., Stedman's Medical Dictionary (1990) (copy enclosed). Thus, the term "ligand precursor" would

be understood by an ordinary artisan to mean a compound that itself cannot activate a nuclear receptor, but is capable of being converted to an active compound that binds and activates a nuclear receptor. This meaning of the term is also made clear by the discussion and examples of ligand precursors disclosed throughout the application, e.g., at page 14, lines 8-12 and 15-22. Thus, the scope of the claims would thus be clear to one of ordinary skill in the art, guided by the specification. Accordingly, Applicants respectfully request that this ground of rejection be withdrawn.

Rejections Under 35 U.S.C. §102

Claims 9 and 11 are rejected as anticipated by Zhao et al. (Zhao). Zhao uses a two-hybrid system to test the ability of certain ligands (vitamin D analogs) to bind and activate the vitamin D receptor (a nuclear receptor).

This rejection is respectfully traversed. Claim 9 requires evaluating the ability of a test gene to convert an inactive ligand precursor into an active ligand (i.e., into a compound that binds to and activates a nuclear receptor). Claim 11 requires evaluating the ability of a test gene to convert an inactive form of vitamin D3 into an active form that activates the vitamin D receptor. As discussed above, a ligand precursor is an inactive compound capable of being converted to an active ligand that binds and activates a nuclear receptor. The Examiner contends that the vitamin D analogs of Zhao can be considered ligand precursors (see office action, page 4, line 1). However, Zhao uses a two-hybrid system to evaluate the ability of vitamin D analogs to bind and activate the vitamin D receptor directly. (As the Examiner correctly notes in the office action, page 4, line 1, Zhao's "analogs bind to the nuclear receptor.") In other words, the vitamin D analogs of Zhao are active ligands of vitamin D receptor, as a ligand is defined in the present specification. Zhao does not teach or suggest the conversion of any ligand precursor (an inactive form) into a ligand. Much less does Zhao disclose or suggest evaluating the ability of any test gene to convert an inactive ligand precursor into an active ligand, as required by the claims. Thus, the present claims are not anticipated by Zhao.

Accordingly, Applicants respectfully request that this rejection be withdrawn.

Rejections Under 35 U.S.C. §103

Claims 8-11 are rejected as unpatentable over Moore et al. (Moore). The Examiner provides the following arguments:

> [Moore] involves transfection of a test gene into cell, treating a cell with a ligand, and isolating the positive clones. . .[Moore] further discloses[that] the methods can be practiced using the VDR as a heterodimer partner [with] the RXR receptor. . . Thus, it would have been obvious to [one] of skill in the art at the time the invention was made to practice the method taught by [Moore] involves transfection of a test gene into a cell, treating a cell with a ligand, and isolating the positive clones.

This rejection is respectfully traversed. To establish prima facie obviousness of a claimed invention, "the prior art reference (or references when combined) must teach or suggest all the claim limitations" (see MPEP § 706.02(j), emphasis added). In addition, there must be a motivation to combine or modify the reference(s) to arrive at the claimed invention, and a reasonable expectation of success. Here, a prima facie case of obviousness has not been made because Moore lacks a teaching, suggestion or motivation to perform a method wherein the ability of a test gene to convert an inactive ligand precursor into an active ligand is evaluated.

Moore discloses a method of identifying proteins that interact with retinoid X receptor (RXR) in a ligand dependent manner. The Moore method includes evaluating whether a test protein increases expression of a reporter gene as an indication of its ability to interact with the RXR (see, e.g., Moore abstract and pages 2-3). Thus, the test proteins of Moore are active ligands, as they bind and activate the RXR. Moore does not disclose or suggest the conversion of any ligand precursor (an inactive form) into a ligand, as recited in the claims. Indeed, Moore does not even disclose or suggest any ligand precursor as that term is used in Applicants' specification. Nor does the Examiner assert that Moore discloses a ligand precursor, as the Examiner merely states that Moore discloses "treating a cell with a ligand" (emphasis added). The "test gene" of Moore to which the Examiner refers is apparently from the liver cDNA library discussed on page 12 of Moore. Each of these library members was fused to a transcriptional activation domain and tested for binding activity. Thus, Moore's "test genes" provide the ligands themselves. Moore's system is not set up to seek test genes that encode a protein that converts a precursor into a ligand, as presently claimed. Therefore, the first criterion for a prima

facie case of obviousness has not been met, as the cited reference does not disclose all the limitations of the claims.

Furthermore, the second and third criteria for a prima facie case of obviousness are also lacking because the Examiner has not provided a motivation or a reasonable expectation of success for one of ordinary skill in the art to modify Moore in any way, much less in a manner as to arrive at the claimed methods. The Examiner's merely conclusory statement that the claimed methods would have been obvious is, of course, not sufficient to provide the required motivation. Accordingly, a prima face case of obviousness has not been made and Applicants respectfully request that the rejection be withdrawn.

Attached is a marked-up version of the changes being made by the current amendment.

Applicant asks that all claims be allowed. Enclosed is a Petition for Extension of Time with the required fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: October 18, 2002

Leda Lucero, Reg. No. 50,635
for: Janis K. Fraser
Reg. No. 34,819

Fish & Richardson P.C.
225 Franklin Street
Boston, Massachusetts 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

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Version with markings to show changes made

In the claims:

Claims 8-11 have been amended as follows:

8. (Twice Amended) A method for screening for a gene encoding a polypeptide that converts a ligand precursor into a ligand, the method comprising

(A) introducing a test gene into a cell comprising (i) a vector comprising a nucleic acid sequence encoding a nuclear receptor and (ii) a vector comprising a binding sequence to which the nuclear receptor binds and, located downstream of the binding sequence, a nucleic acid sequence encoding a reporter molecule,

(B) contacting a ligand precursor with the cell into which the test gene is introduced,

(C) evaluating the activity of the reporter molecule relative to the activity of the reporter in the absence of the test gene, an increase in activity indicating that the test gene encodes a polypeptide that converts the ligand precursor into a ligand that activates the nuclear receptor; and

(D) isolating the test gene from the cell if the cell shows an increase in reporter activity.

9. (Twice Amended) A method for determining whether or not a test gene encodes a polypeptide that converts a ligand precursor into a ligand, the method comprising

(A) introducing a test gene into a cell comprising (i) a vector comprising a nucleic acid sequence encoding a nuclear receptor and (ii) a vector comprising a binding sequence to which the nuclear receptor binds and, located downstream of the binding sequence, a nucleic acid sequence encoding a reporter molecule,

(B) contacting a ligand precursor with the cell into which the test gene is introduced, and

(C) evaluating the activity of the reporter molecule relative to the activity of the reporter in the absence of the test gene, an increase in activity indicating that the test gene encodes a polypeptide that converts the ligand precursor into a ligand that activates the nuclear receptor.

10. (Twice Amended) A method for screening for a gene encoding a polypeptide that converts an inactive form of vitamin D3 into an active form, the method comprising

(A) introducing a test gene into a cell comprising (i) a vector comprising a nucleic acid sequence encoding a vitamin D receptor and (ii) a vector comprising a binding sequence of the vitamin D receptor and, located downstream of the binding sequence, a nucleic acid sequence encoding a reporter molecule,

(B) contacting an inactive form of vitamin D3 with the cell into which the test gene is introduced,

(C) evaluating the activity of the reporter molecule relative to the activity of the reporter in the absence of the test gene, an increase in activity indicating that the test gene encodes a polypeptide that converts an inactive form of vitamin D3 into an active form that activates the vitamin D receptor, and

(D) isolating the test gene from the cell if the cell shows an increase in reporter activity.

11. (Twice Amended) A method for determining whether or not a test gene encodes a polypeptide that converts an inactive form of vitamin D3 into an active form, the method comprising

(A) introducing a test gene into a cell comprising (i) a vector comprising a nucleic acid sequence encoding a vitamin D receptor and (ii) a vector comprising a binding sequence to which vitamin D receptor and, located downstream of the binding sequence, a nucleic acid sequence encoding a reporter binds molecule,

(B) contacting an inactive form of vitamin D3 with the cell into which the test gene is introduced, and

(C) evaluating the activity of the reporter molecule relative to the activity of the reporter in the absence of the test gene, an increase in activity indicating that the test gene encodes a polypeptide that converts an inactive form of vitamin D3 into an active form that activates the vitamin D receptor.

Stedman's
MEDICAL DICTIONARY

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Printed in the United States of America

English Language Co-editions
Asian 1967, 1972, 1976
Indian 1967, 1973
Taiwan 1972, 1978

Translated Editions
Greek 1976
Indian 1977
Japanese 1977, 1985
Portuguese 1976
Spanish (in press)

Library of Congress Cataloging-in-Publication Data

Stedman, Thomas Lathrop, 1853–1938.
[Medical dictionary]
Stedman's medical dictionary.—25th ed.
p. cm.
ISBN 0-683-07916-6
1. Medicine—Dictionaries. I. Title. II. Title: Medical dictionary
[DNLM: 1. Dictionaries, Medical. W 13 S812m]
R121.S8 1989
610'.3—dc20
DNLM/DLC
for Library of Congress

89-16579
CIP

89 90 91 92 93 94
1 2 3 4 5 6 7 8 9 10

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preconscious (prē-kon'shŭs). In psychoanalysis, one of the three divisions of the psyche according to Freud's topographical psychology, the other two being the conscious and unconscious; includes all ideas, thoughts, past experiences, and other memory impressions that with effort can be consciously recalled. *Cf.* foreconscious.

preconvulsive (prē-kon-vŭl'siv). Denoting the stage in an epileptic paroxysm preceding convulsions.

precordia (prē-kōr'dē-ă) [L. *praecordia* (ntr. pl. only), the diaphragm, the entrails, fr. *prae,* before, + *cor* (*cord-*), heart]. Antecardium; the epigastrium and anterior surface of the lower part of the thorax.

precordial (prē-kōr'dē-ăl). Relating to the precordia.

precordialgia (prē'kōr-dē-al'jē-ă) [precordia + G. *algos,* pain]. Pain in the precordial region.

precordium (prē-kōr'dē-ŭm). Singular of precordia.

precostal (prē-kos'tăl) [pre- + L. *costa,* rib]. Anterior to the ribs.

precritical (prē-krit'i-kăl). Relating to the phase before a crisis.

precuneal (prē-kū'nē-ăl). Anterior to the cuneus.

precuneate (prē-kū'nē-āt). Relating to the precuneus.

precuneus (prē-kū'nē-ŭs) [pre- + L. *cuneus,* a wedge]]NA]. Quadrate lobe (3); quadrate lobule (2); lobulus quadratus (2); quader; a division of the medial surface of each cerebral hemisphere between the cuneus and the paracentral lobule; it lies above the subparietal sulcus and is bounded anteriorly by the pars marginalis of the sulcus cinguli and posteriorly by the parietooccipital sulcus.

precursor (prē-ker'ser) [L. *praecursor,* fr. *prae-,* pre- + *curro,* to run]. That which precedes another or from which another is derived, applied especially to a physiologically inactive substance that is converted to an active enzyme, vitamin, hormone, etc., or to a chemical substance that is built into a larger structure in the course of synthesizing the latter.

predecidual (prē-dē-sid'yū-ăl). Relating to the premenstrual or secretory phase of the menstrual cycle.

predentin (prē-den'tin). The organic fibrillar matrix of the dentin before its calcification.

prediabetes (pre'dī-ă-bē'tēz). A state of potential diabetes mellitus, with normal glucose tolerance but with an increased risk of developing diabetes.

prediastole (prē-dī-as'tō-lē). Late systole; the interval in the cardiac rhythm immediately preceding the diastole.

prediastolic (prē-dī-ă-stol'ik). Late systolic; relating to the interval preceding the cardiac diastole.

predicrotic (prē-dī-krot'ik). Preceding the dicrotic notch.

predigestion (prē-dī-jes'chŭn). The artificial initiation of digestion of proteins (proteolysis) and starches (amylolysis) before they are eaten.

predispose (prē'dis-pōz). To render susceptible.

predisposition (prē'dis-pō-zish'ŭn). A condition of special susceptibility to a disease.

prednisolone (pred-nis'ō-lōn). Metacortandrolone; Δ^1-dehydrocortisol; Δ^1-hydrocortisone; hydroretrocortine; 11β,17,21-trihydroxy-1,4-pregnadiene-3,20-dione; a dehydrogenated analogue of cortisol with the same actions and uses as cortisol.

p. acetate, prednisolone 21-acetate; same uses as p.; suitable for intramuscular administration.

p. butylacetate, p. tebutate.

p. sodium phosphate, prednisolone 21-(disodium phosphate); more soluble than p. and the other p. esters and useful when a rapid onset or a short duration of action is desired; suitable for intrasynovial, parenteral, and topical administration.

p. succinate, p. compound suitable for intramuscular, intravenous, or rectal administration.

p. tebutate, p. butylacetate; same actions and uses as p. but with longer duration of action and suitable for intrasynovial and soft tissue injection.

prednisone (pred'ni-sōn). Metacortandracin; deltacortisone; Δ^1-cortisone; retrocortine; 17α,21-dihydroxy-1,4-pregnadiene-3,11,20-trione; a dehydrogenated analogue of cortisone with the same actions and uses.

prednylidene (prēd-nil'i-dēn). 16-Methyleneprednisolone; 11β,17,21-trihydroxy-16-methylenepregna-1,4-diene-3,20-dione; a glucocorticoid.

predormital (prē-dōr'mi-tăl). Pertaining to the predormitum.

predormitum (prē-dōr'mi-tŭm). [pre- + L. *dormire,* to sleep]. The stage of semi-unconsciousness preceding actual sleep.

preductal (prē-dŭk'tăl). Relating to that part of the aorta proximal to the aortic opening of the ductus arteriosus.

preeclampsia (prē-ē-klamp'sē-ă) [pre- + G. *eklampsis,* a shining forth (eclampsia)]. Development of hypertension with proteinuria or edema, or both, due to pregnancy or the influence of a recent pregnancy; it occurs after the 20th week of gestation, but may develop before this time in the presence of trophoblastic disease; it is predominantly a disorder of primigravidas.

superimposed p., superimposed eclampsia; the development of p. or eclampsia in a patient with chronic hypertensive vascular or renal disease; when the hypertension antedates the pregnancy as established by previous blood pressure recordings, a rise in the systolic pressure of 30 mm Hg or a rise in the diastolic pressure of 15 mm Hg and the development of proteinuria or edema, or both, are required during pregnancy to establish the diagnosis.

preepiglottic (prē'ep-i-glot'ik). Anterior to the epiglottis.

preeruptive (prē-e-rŭp'tiv). Denoting the stage of an exanthematous disease preceding the eruption.

preexcitation (prē'ek-sī-tā'shŭn). Premature activation of part of the ventricular myocardium by an impulse that travels by an anomalous path and so avoids physiological delay in the atrioventricular junction; an intrinsic part of the Wolff-Parkinson-White syndrome.

preformation (prē-fōr-mā'shŭn). See preformation *theory.*

prefrontal (prē-fron'tăl). **1.** Denoting the anterior portion of the frontal lobe of the cerebrum. **2.** Denoting the granular frontal cortex rostral to the premotor area.

preganglionic (prē'gang-glē-on'ik). Situated proximal to or preceding a ganglion; referring specifically to the preganglionic motor neurons of the autonomic nervous system (located in the spinal cord and brainstem) and the preganglionic, myelinated nerve fibers by which they are connected to the autonomic ganglia.

pregnancy (preg'nan-sē) [L. *praegnans* (*praegnant-*), pregnant, fr. *prae,* before, + *gnascor,* pp. *natus,* to be born]. Gestation; fetation; cyesis, graviditas; gravidism; the condition of a female after conception until the birth of the baby.

abdominal p., intraperitoneal p.; abdominocyesis (1); the implantation and development of the ovum in the peritoneal cavity, usually secondary to an early rupture of a tubal p.; very rarely, primary implantation may occur in the peritoneal cavity.

aborted ectopic p., tubal *abortion.*

ampullar p., tubal p. situated near the midportion of the oviduct.

bigeminal p., twin p.

cervical p., the implantation and development of the impregnated ovum in the cervical canal.

combined p., coexisting uterine and ectopic p.

compound p., development of a uterine p. in addition to a previously existing ectopic pregnancy (usually a lithopedion).

cornual p., the implantation and development of the impregnated ovum in one of the cornua of the uterus.